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Applicant: Hoechst AG, 6000 Frankfurt

Inventor: Otto, Eberhard, Dr., 6233 Kelkheim; Muschaweck, Roman, Dr., 6230 Frankfurt

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HOECHST AKTIENGESELLSCHAFT

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Sulphamates, and a process for their production

The present invention concerns sulphamates with general formula I:

$Ar\text{-}O\text{-}SO_2\text{-}NH_2$ (I)

in which Ar represents a phenyl residue monosubstituted in the 2-position by a methyl group or a halogen atom, in the 2- or 3-position by a methoxy group, in the 3- and 5- position by 2 halogen atoms, or in any position by alkyl or alkoxy groups containing 2-4 C atoms, or disubstituted in any position by 2 alkyl groups containing 2-4 C-atoms, 2 alkoxy groups, 2 aralkoxy groups containing 1-4 C-atoms in the alkyl portion or an alkylenedioxy group containing 1-4 C atoms, or a 1- or 2-naphthyl residue.

The invention also concerns a process for the production of aryl sulphamates with general formula II:

$Ar'\text{-}O\text{-}SO_2\text{-}NH_2$ (II)

in which Ar' represents a phenyl residue mono- or di-substituted in any position by alkyl-, alkoxy- or alkylenedioxy groups containing 1-4 C atoms or by halogen atoms, or a 1- or 2-naphthyl residue, characterized in that a phenol, Ar'-OH, in which Ar' has the meanings given above, is reacted with sulphamic acid chloride in an organic solvent in the presence of a base.

The production of aryl sulphamates by reacting phenols with N-chlorosulphonyl isocyanate to produce chlorosulphonyl urethanes and rearranging to form phenoxysulphonylisocyanates with subsequent hydration followed by decarboxylation is

already known (DE-1 593 846). Not only does this synthetic pathway necessitate 3 steps, but also, when the rearrangement to the phenoxysulphonylisocyanate is carried out, side reactions can occur, for example intramolecular ring closure, if the phenols employed have a free ortho-position. This is a particularly prevalent side reaction in the case of alkylphenols and alkoxyphenols (Lohaus, Chem. Ber. 105, 2791 (1972).

The process of the invention requires just one reaction step to produce the aryl sulphamate, in which step the corresponding phenol is reacted at about 40°C in an inert organic solvent with an excess of sulphamic acid chloride and a base. Operating at a lower temperature avoids ortho- substitution as a side reaction.

The process of the invention is surprisingly simple to carry out, has no side reactions and thus constitutes a considerable advantage over known processes.

In accordance with the invention, the following phenols, Ar'-OH, can be used as starting materials in the process of the invention:

Phenol, 2-methoxyphenol, 3-methoxyphenol, 4-methoxyphenol, all dimethoxyphenol isomers, 2-benzyloxyphenol, 3-benzyloxyphenol, 4-benzyloxyphenol, all bis-(benzyloxy)-phenol isomers, all methylenedioxyphenol isomers, ethylenedioxyphenol isomers, 2-methylphenol, 3-methylphenol, 4-methylphenol, all isomers of dimethylphenols, 2-chlorophenol, 3-chlorophenol, 4-chlorophenol, all dichlorophenol isomers, and also 1-naphthol and 2-naphthol.

The following variously substituted phenols can also be considered for use as starting materials:

2-methoxy-3-methylphenol, 2-methoxy-4-methylphenol, 2-methoxy-3-chlorophenol, 2-methoxy-4-chlorophenol, 3-methoxy-2-methylphenol, 3-methoxy-4-methylphenol, 3-methoxy-2-chlorophenol, 3-methoxy-4-chlorophenol, 4-methoxy-2-methylphenol, 4-methoxy-3-methylphenol, 4-methoxy-2-chlorophenol, 4-methoxy-3-chlorophenol, 3,5-

dimethoxy-2-methylphenol, 2,5-dimethoxy-4-methylphenol, 3,5-dimethoxy-2-chlorophenol, 2,5-dimethoxy-4-chlorophenol, 2,3-methylenedioxy-4-methylphenol, 2,3-methylenedioxy-5-methylphenol, 2,3-methylenedioxy-6-methylphenol, 2,3-methylenedioxy-4-chlorophenol, 2,3-methylenedioxy-5-chlorophenol, 2,3-methylenedioxy-6-chlorophenol, 3,4-methylenedioxy-2-methylphenol, 3,4-methylenedioxy-5-methylphenol, 3,4-methylenedioxy-6-methylphenol, 3,4-methylenedioxy-2-chlorophenol, 3,4-methylenedioxy-5-chlorophenol, 3,4-methylenedioxy-6-chlorophenol, 2,3-ethylenedioxy-4-methylphenol, 2,3-ethylenedioxy-5-methylphenol, 2,3-ethylenedioxy-6-methylphenol, 2,3-ethylenedioxy-4-chlorophenol, 2,3-ethylenedioxy-5-chlorophenol, 2,3-ethylenedioxy-6-chlorophenol, 3,4-ethylenedioxy-2-methylphenol, 3,4-ethylenedioxy-5-methylphenol, 3,4-ethylenedioxy-6-methylphenol, 3,4-ethylenedioxy-2-chlorophenol, 3,4-ethylenedioxy-5-chlorophenol, 3,4-ethylenedioxy-6-chlorophenol.

Advantageously, the reaction is carried out by adding a solution of phenol and base dropwise into a solution of sulphamic acid chloride so that the latter solution is slightly heated by the resulting heat of reaction.

In general, the reaction is carried out in an inert organic solvent, preferably methylene chloride or benzene. However, carbon tetrachloride, toluene, dioxane or tetrahydrofuran can also be used, for example. Preferred examples of bases are tertiary organic bases, preferably triethylamine, pyridine or N-methylpiperidine.

The reaction mixture is then worked up, whereby the solution obtained is extracted with 2N HCl, optionally after adding a second solvent, then dried and concentrated. The crude product then precipitates out. In most cases, the crude products are then purified by re-crystallisation from a suitable solvent such as toluene. Purification can also be carried out by column chromatography.

In addition to the compounds mentioned in the examples, the following compounds can be prepared in accordance with claim 2:

2-methoxyphenyl sulphamate;

3-methoxyphenyl sulphamate;

4-methoxyphenyl sulphamate;

2,3-dimethoxyphenyl sulphamate;

2,4-dimethoxyphenyl sulphamate;

2,5-dimethoxyphenyl sulphamate;

2,6-dimethoxyphenyl sulphamate;

3,4-dimethoxyphenyl sulphamate;

3,5-dimethoxyphenyl sulphamate;

and corresponding compounds in which the "dimethoxy" portion is replaced by "diethoxy";

2-benzyloxyphenyl sulphamate;

3-benzyloxyphenyl sulphamate;

4-benzyloxyphenyl sulphamate;

2,3-bis(benzyloxy)phenyl sulphamate;

2,4-bis(benzyloxy)phenyl sulphamate;

2,5-bis(benzyloxy)phenyl sulphamate;

2,6-bis(benzyloxy)phenyl sulphamate;

3,4-bis(benzyloxy)phenyl sulphamate;

3,5-bis(benzyloxy)phenyl sulphamate;

2,3-methylenedioxyphenyl sulphamate;

3,4-methylenedioxyphenyl sulphamate;

2,3-ethylenedioxyphenyl sulphamate;

3,4-ethylenedioxyphenyl sulphamate;

2-methylphenyl sulphamate;

3-methylphenyl sulphamate;

4-methylphenyl sulphamate;

2,3-dimethylphenyl sulphamate;

2,4-dimethylphenyl sulphamate;

2,5-dimethylphenyl sulphamate;

2,6-dimethylphenyl sulphamate;

3,4-dimethylphenyl sulphamate;

3,5-dimethylphenyl sulphamate;

2-chlorophenyl sulphamate;

3-chlorophenyl sulphamate;

4-chlorophenyl sulphamate;

2,3-dichlorophenyl sulphamate;

2,4-dichlorophenyl sulphamate;

2,5-dichlorophenyl sulphamate;

2,6-dichlorophenyl sulphamate;

3,4-dichlorophenyl sulphamate;

3,5-dichlorophenyl sulphamate;

1-naphthyl sulphamate;

2-naphthyl sulphamate;

2-methoxy-3-methylphenyl sulphamate;

2-methoxy-4-methylphenyl sulphamate;

2-methoxy-3-chlorophenyl sulphamate;

2-methoxy-4-chlorophenyl sulphamate;

3-methoxy-2-methylphenyl sulphamate;

3-methoxy-4-methylphenyl sulphamate;

3-methoxy-2-chlorophenyl sulphamate;

3-methoxy-4-chlorophenyl sulphamate;

4-methoxy-2-methylphenyl sulphamate;

4-methoxy-3-methylphenyl sulphamate;

4-methoxy-2-chlorophenyl sulphamate;

4-methoxy-3-chlorophenyl sulphamate;

3,5-dimethoxy-2-methylphenyl sulphamate;

3,5-dimethoxy -4-methylphenyl sulphamate;

3,5-dimethoxy -2-chlorophenyl sulphamate;

3,5-dimethoxy -4-chlorophenyl sulphamate;

and corresponding compounds in which the "dimethoxy" portion is replaced by "diethoxy";

2,3-methylenedioxy-4-methylphenyl sulphamate;

2,3-methylenedioxy-5-methylphenyl sulphamate;

2,3-methylenedioxy-6-methylphenyl sulphamate;

2,3-methylenedioxy-4-chlorophenyl sulphamate;

2,3-methylenedioxy-5-chlorophenyl sulphamate;

2,3-methylenedioxy-6-chlorophenyl sulphamate;

3,4-methylenedioxy-2-methylphenyl sulphamate;

3,4-methylenedioxy-5-methylphenyl sulphamate;

3,4-methylenedioxy-6-methylphenyl sulphamate;

3,4-methylenedioxy-2-chlorophenyl sulphamate;

3,4-methylenedioxy-5-chlorophenyl sulphamate;

3,4-methylenedioxy-6-chlorophenyl sulphamate;

2,3-ethylenedioxy-4-methylphenyl sulphamate;

2,3-ethylenedioxy-5-methylphenyl sulphamate;

2,3-ethylenedioxy-6-methylphenyl sulphamate;

2,3-ethylenedioxy-4-chlorophenyl sulphamate;

2,3-ethylenedioxy-5-chlorophenyl sulphamate;

2,3-ethylenedioxy-6-chlorophenyl sulphamate;

3,4-ethylenedioxy-2-methylphenyl sulphamate;

3,4-ethylenedioxy-5-methylphenyl sulphamate;

3,4-ethylenedioxy-6-methylphenyl sulphamate;

3,4-ethylenedioxy-2-chlorophenyl sulphamate;

3,4-ethylenedioxy-5-chlorophenyl sulphamate;

3,4-ethylenedioxy-6-chlorophenyl sulphamate.

In addition to the compounds mentioned in the examples, the following compounds can be prepared in accordance with claim 1:

3-methoxyphenyl sulphamate;

4-ethoxyphenyl sulphamate;

3,5-diethoxyphenyl sulphamate;

2,3-methylenedioxyphenyl sulphamate;

2,3-ethylenedioxyphenyl sulphamate;

3,4-ethylenedioxyphenyl sulphamate;

2,6-dichlorophenyl sulphamate;

3,4-dichlorophenyl sulphamate;

3,5-dichlorophenyl sulphamate.

The novel sulphamates are good diuretics with an exceptional carbonic anhydrase inhibitor effect.

The products of the invention constitute valuable therapeutic substances suitable for producing diuresis by carbonic anhydrase inhibition (treatment of glaucoma).

They can be administered as is or together with the usual galenical excipients in the form of tablets, dragees, capsules, solutions or suspensions.

The quantity of active ingredient is 50 mg to 1000 mg, preferably 100-500 mg.

For parenteral use, solutions or suspensions in water are preferred. However, other physiologically acceptable solvents can also be used, for example ethanol, as well as solubilizers.

A combination with other active ingredients is also possible. Examples of substances that can be used in combination, for example antihypertensives, are:

reserpine, dihydralazine, guanethidine, guanacline, clonidine.

Examples:

The novel aryl sulphamates were characterized by their melting points.

Example 1

phenyl sulphamate

70 g (0.6 mole) of sulphamic acid chloride was dissolved in 500 ml of dry methylene chloride. A solution of 18.8 g (0.2 mole) of phenol and 60.6 g (0.6 mole) of triethylamine in 300 ml of dry methylene chloride was added to that solution over a period of 10 minutes. The solution heated up to about 40°. It was stirred at ambient temperature for 2 days and the methylene chloride was evaporated off under vacuum. 2N HCl was added to the residue and then extracted several times with ether. The combined ether extracts were dried and concentrated. 18.4 g of phenyl sulphamate was obtained. MP 86° (from toluene).

Example 2

p-methoxyphenyl sulphamate

23 g (0.2 mole) of sulphamic acid chloride was dissolved in 200 ml of absolute benzene. A solution of 6.2 g (0.05 mole) of p-methoxyphenol and 20.2 g (0.2 mole) of triethylamine in 100 ml of dry benzene was added to that solution over a period of 30 minutes. The solution heated up slightly during the dropwise addition; it was stirred at ambient temperature for 3 days; the benzene was evaporated off under vacuum; 2N HCl was added and several extractions were carried out with ethyl acetate. The combined ethyl acetate extracts were dried and concentrated. After adding cyclohexane, 3.3 g of p-methoxyphenyl sulphamate was obtained with a MP of 65°.

Example 3

ortho-methoxyphenyl sulphamate

The method of Example 1 was followed, and the residue was recrystallised from isopropylether/cyclohexane. 9.8 g of orthomethoxyphenyl sulphamate was obtained with a melting point of 78°.

Example 4

para-benzyloxyphenyl sulphamate

The method of Example 1 was followed, with the exception that four equivalents of a sulphamic acid chloride and triethylamine were used.

The ether residue was re-crystallised twice from toluene. 19 g of p-benzyloxyphenyl sulphamate was obtained with a melting point of 121°.

Example 5

p-chlorophenyl sulphamate

The method of Example 1 was followed to produce 22 g of p-chlorophenylsulphamate with a melting point of 104°.

Example 6

3,4-methylenedioxyphenyl sulphamate

460 g (4 mole) of sulphamic acid chloride was dissolved in 1 l of dry methylene chloride. A solution of 70 g (0.5 mole) of 3,4-methylenedioxyphenol and 412 g (4.0 mole) of triethylamine in one litre of dry methylene chloride was added dropwise to that solution over a period of 2 hours. The solution heated up to 40° and was stirred for a further 3 days. The solvent was evaporated off under vacuum, the residue was supplemented with 2N HCl and extracted several times with methylene chloride. The methylene chloride was dried and evaporated to dryness. The remaining oil (63 g) was separated on a silica column (1.3 kg) with methylene chloride as the eluent. 50 g of 3,4-methylenedioxyphenyl sulphamate with a melting point of 72°was obtained.

Example 7

3,5-dimethoxyphenyl sulphamate

The method of Example 1 was followed, with the exception that 2 equivalents of sulphamic acid chloride and triethylamine were used. The ether residue was taken up in methanol and the 3,5-dimethoxyphenyl sulphamate precipitated out on adding water. 12.5 g was obtained; melting point 111°.

Example 8

2,6-dimethylphenyl sulphamate

The method of Example 4 was followed to produce 16 g of 2,6-dimethylphenyl sulphamate with a melting point of 109° after re-crystallisation from toluene.

Example 9

2-naphthyl sulphamate

The method of Example 4 was followed to produce 12 g of 2-naphthyl sulphamate with a melting point of 112° after re-crystallisation from toluene.

Example 10

1-naphthyl sulphamate

The method of Example 4 was followed to produce 7 g (16%) of 1-naphthyl sulphamate with a melting point of 98° after re-crystallisation from toluene.

CLAIMS

1. Sulphamates with general formula I:

$Ar\text{-}O\text{-}SO_2\text{-}NH_2$ (I)

in which Ar represents a phenyl residue monosubstituted in the 2-position by a methyl group or a halogen atom, in the 2- or 3-position by a methoxy group, in the 3- and 5-position by 2 halogen atoms, or in any position by alkyl or alkoxy groups containing 2-4 C atoms, or disubstituted in any position by 2 alkyl groups containing 2-4 C-atoms, 2 alkoxy groups, 2 aralkoxy groups containing 1-4 C-atoms in the alkyl portion or an alkylenedioxy group containing 1-4 C atoms, or a 1- or 2-naphthyl residue.

2. A process for the production of sulphamates with general formula II:

$Ar'\text{-}O\text{-}SO_2\text{-}NH_2$ (II)

in which Ar' represents a phenyl residue mono- or di-substituted in any position by alkyl-, alkoxy- or alkylenedioxy groups containing 1-4 C atoms or by halogen atoms, or a 1- or 2-naphthyl residue, characterized in that a phenol, Ar'-OH, in which Ar' has the meanings given above, is reacted with sulphamic acid chloride in an organic solvent in the presence of a base.

3. A process for the production of pharmaceutical preparations with a diuretic effect, characterized in that compounds with general formula II in which Ar' has the meanings given in claim 2, optionally together with pharmaceutically acceptable carriers and/or stabilisers, are made into a form suitable for therapeutic use.

4. Pharmaceutical preparations with a diuretic effect containing or consisting of compounds with general formula II:

$Ar'\text{-}O\text{-}SO_2\text{-}NH_2$ (II)

in which Ar' has the meanings given in claim 2.

5. Pharmaceutical preparations containing or consisting of a combination of compounds with general formula II, in which Ar' has the meanings given in claim 2, with antihypertensive compounds.